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10/084,960	02/28/2002	Jurgen Hescheler	Isar Patent 1084.1-KGB	3201

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,960	HESCHELER, JURGEN	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-41 and 54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-40, 54-62* is/are rejected.

7)☒ Claim(s) *41 and 63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed February 28, 2002 is a continuation of 09/446,717 filed 04/13/2000, now abandoned, which is a national stage entry of PCT/EP98/03988 with the international filing date of June 30, 1998.

Applicant's amendment filed January 13, 2005, has been received and entered. Claims 1-31, 42-53 have been canceled. Claim 41 has been amended. Claims 54-63 have been added. Claims 32-41, 54-63 are pending.

It is noted that the editor marks for claim 41 are not complete, in that "α" is being added to the claim.

Election/Restrictions

Applicant's election without traverse of Group I, claims 32–41, in the reply filed on June 3, 2004 was acknowledged (bottom of page 4). Newly added claims are drawn to the elected invention. Claims 32-41, 54-63 drawn to a cell culture cell-type or development-specific expression of a fluorescent protein are currently under examination.

Priority

Applicants indicate that a translation of the foreign language application is not required under 35 USC 371. See page 5 of Applicant's amendment.

Examiner agrees with Applicant's remarks. Examiner's note that a translation of the foreign application should be submitted under 37 CFR 1.55 is required to gain benefit of foreign priority under 35 U.S.C. 119(a)-(d) is not applicable in the instant case.

Claim Objections

Claim 41 objected to because pCX-(a-act)GFP-Neo is misspelled and should be set forth as pCX-(**α**-act)GFP-Neo or pCX-(**alpha**-act)GFP-Neo is withdrawn.

The amendment to claim 41 to recite pCX-([[a]]**α**-act)GFP-Neo is consistent with promoters discussed in the specification.

Response to Amendment

The declaration of Dr. Jurgen Hescheler filed February 9, 2004 has been considered. It will be discussed in detail below in view of the rejections made in view of the teachings of Zernicka-Goetz *et al.* and further references cited in the rejection made under 35 USC 103.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 41 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Applicant notes that the undersigned attorney provides verification the deposit was made in accordance with the Budapest Treaty in Appendix A (page 5 and Appendix A filed November 29, 2004).

Evidence that the deposit has been made under the terms of the Budapest Treaty, and the declaration by the attorney of record over his or her signature and registration number, stating that the specific cell lines have been deposited under the Budapest Treaty and that the cell lines will be irrevocably and without restriction released to the public upon the issuance of a patent, satisfies the deposit requirement.

It is noted that newly added claims 63 encompasses the same deposited vector.

Claims 32-35, 39 and 40 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant notes that the previous amendment pointed to several portions of the specification for supporting the claim amendment (page 6). Applicant argues that literal support for an amendment need not be present in a specification, only that claimed embodiments are described citing *In re Lukach, In re Wertheim* and *In re Ruschig* in support of their argument (page 6). Applicant's arguments have been fully considered, but not found persuasive.

As noted previously, there is no literal support for "is substantially inactive in undifferentiated embryonic stem cells" in any portions of the cited passages of the specification.

Importantly, there is no teaching nor discussion on what is "substantially inactive" to determine the metes and bounds of this embodiment relative to the claimed invention. The portions of the specification on pages 4 and 6, each detail expression in an ES cell in which a promoter is activated, and provides no basis for what expression was present in the ES cell before activation, and importantly what one would consider substantially inactive in the ES cell. Page 12 of the specification is taken from the specific working example number 2, where the alpha-actin promoter has been reduced to practice. As described in the specification and acknowledged in the art, the alpha-actin promoter is considered a cardiac specific promoter, however the working example clearly demonstrates that the promoter is active in ES cells, albeit at levels that are lower than those found in a cardiac cell. In light of the cited passages and the specification as a whole, the issue remains to what is considered substantially inactive. This can be distinguished from the embodiment of newly added claims 54-63 which encompass "activated after differentiation of the stem cells" because there is no unique requirements of the activity of the promoter before being activated. The embodiment of a promoter that "is substantially inactive in undifferentiated embryonic stem cells" is not clearly described in the instant specification, nor are any specific methods for clearly identifying promoters that meet this limitation. The single working example provided in support of this embodiment demonstrates that the promoter is active in ES cells, without providing any guidance to the particular activity observed in the ES cell and how this is to be viewed as representatively substantially inactive to obtain other promoters.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, claim 32

recites that the promoter used, and Applicants amendment does not point to support in the specification for this new embodiment. Upon review of the specification Examiner can not find literal support for this embodiment, and while some of the specific examples of promoters provided in the specification may meet this limitation, it does not appear that this limitation was specifically contemplated.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 32-35, 39 and 40 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described. As discussed above, because there is no specific guidance to what is considered substantially inactive, it would be considered undue experimentation without any expectation of success of determining whether a promoter would be considered substantially inactive in ES cells. This can be distinguished from promoters that should not be active at all in ES cells. In this case, this is the reason that claims with the recitation of promoters active in specific differentiated cells have not been included in the basis of the rejection. Each of these specific promoters should not be active in ES cells. In the case of the alpha-actin promoter and the pCX-(α-act)GFP-Neo construct, each of these has its own inherent promoter activites. While it may be argued to whether it meets the limitation of "substantially inactive", they are clearly described and enabled in the present specification for use to the extent they have inherent activities as promoters. It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013

(Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). In this case, without any guidance to what is substantially inactive, the specification fails to provide the necessary guidance and description of the promoters as broadly claimed.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claim Rejections - 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32, 33, 35, 36, 39 and 40 stand rejected and newly added claims 54, 55, 57, 61 and 62 are under 35 U.S.C. 102(b) as being clearly anticipated by Zernicka-Goetz *et al.*

Applicant notes that the claims require that the promoter be substantially inactive in ES cells, and argue that the cdc2 promoter fails to meet this limitation because it is active, and only inactive in differentiated cells. Further, the declaration of Dr. Jurgen Hescheler filed February 9, 2004 provides arguments that the cdc2 promoter would not be considered substantially inactive in an ES cell, thus fails to meet all the limitations of the claims. See Applicant's amendment pages 7-8, section 3. Applicant's arguments and declaration have been fully considered, but not found persuasive.

Examiner agrees that the cdc2 promote provides an activity that fails to meet the limitation of substantially inactive in cdc2 cells. However, Zernicka-Goetz *et al.* specifically teaches that the methodology reduced to practice with the cdc2 promoter can be used to study the fate of any cell developed from the ES cell. Importantly, Zernicka-Goetz *et al.* specifically teach that other tissue specific promoters can be used for mapping lineages of specific cell types (bridging pages 1136-1137). In this case, a tissue specific promoter would not be active in a totipotent ES cell, and would be activated after differentiation of the ES cell (newly added claims).

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 33, 35-40 stand rejected and newly added claims 54, 55, 57-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zernicka-Goetz *et al.* in view of Ikawa *et al.* and in further view of Wobus *et al.*, Sartorelli *et al.* and Chen *et al.*

Claims 32-40 stand rejected and newly added claims 54-62 are rejectedunder 35 U.S.C. 103(a) as being unpatentable over Zernicka-Goetz *et al.*, Ikawa *et al.*, Wobus *et al.*, Sartorelli *et al.* and Chen *et al.* in view of Maltsev *et al.* (Circulation Research, 75:233-244) or Rohwedel *et al.* (Developmental Biology 164:87-101).

Applicant summarizes the requirements of making a proper rejection under 35 USC 103 and argue that the Examiner has failed to address all the limitations of the pending claims and to properly address arguments made in a preliminary amendment nor the evidence presented in a declaration of Dr. Jurgen Hescheler also made in a preliminary amendment (pages 8-10). Arguments made in the preliminary amendment are essentially the same as those set forth in the instant amendment. Summarizing the teachings of each of the cited references and the evidence provided in the declaration of Dr. Jugen Hescheler, Applicant argues that the combined references fail to provide the proper motivation and expectation of success to make obvious the claimed invention (pages 10-17). See Applicant's arguments, pages 8-17. Applicants arguments have been fully considered, but not found persuasive.

Initially, it is noted that the declaration of Dr. Jurgen Hescheler and preliminary arguments were filed and focused on previous rejections made in related application and how they would not apply to the filed claims. The evidence and arguments were considered by the Examiner prior to making the rejections of record (Aug. 25, 2004), however were not considered

sufficient in applying the rejection to the instant claims. Both Applicant's instant amendment and information in the declaration will be discussed below. The claims in the prior application were drawn to cell cultures of embryonic stem cells stably transfected with a DNA construct comprising a DNA sequence coding for a non-cell-damaging fluorescent protein operatively linked to a cell-/development-dependent promoter integrated in the native DNA. It was maintained that essentially any promoter, in particular the cd2 promoter would anticipate this limitation because of the definition given in the instant specification. The claims submitted in the instant application were altered from those in the prior application to recite a promoter that is substantially inactive in ES cells and now newly added claims recite that the promoter is activated after differentiations of the stem cells to more clearly indicate that the promoter being used is active or more active in differentiated cells. Dependent claims still set forth use of specific promoters such as the Nkx-2.5, human alpha-actin or MLC-2V promoters.

In view of Applicants arguments regarding motivation and expectation of success, two issues stand out. First, does the art provide motivation and an expectation of success for the use of ES cells to study promoters with a reporter gene, in particular a fluorescent protein, *in vitro* and/or *in vivo*. Second, does the art provide motivation and expectation of success for using the ES to study a variety of promoters. It is noted that it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Further, the test for combining references is not what the individual references

themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988).

In this case, Zernicka-Goetz *et al.* provide clear evidence that the use of the fluorescent protein GFP operatively linked to a heterologous promoter can be successfully inserted and used in ES cells. While Applicant has made arguments and provided references known in the art that fluorescent proteins such as GFP may not be the most effective reporter construct, clearly the results of Zernicka-Goetz *et al.* demonstrate that there is a clear expectation of success for expression of GFP. Further, Zernicka-Goetz *et al.* provides clear evidence that there is an expectation of success that one can study the activity of a heterologous promoter by observing this expression. Zernicka-Goetz *et al.* specifically teach that GFP is an "easily visible and non toxic to mouse cells" (abstract). While the cdc2 promoter is reduced to practice by Zernicka-Goetz *et al.* specifically teach that tissue specific promoters can be used to study the development of a cell starting from the early blastocyst stage (page 1136, bottom of second column for example). Moreover, Zernicka-Goetz *et al.* recognized the problem(s) noted in the art for the use of wild-type GFP (see for example page 1136, Discussion section), and provide a modified form of MmGFP that is clearly functional and better than wild type GFP when used in ES cells. Applicant's arguments that there is no motivation nor expectation of success for the use of flurescent proteins to study the development or fate of an ES cell is not found persuasive because Zernicka-Goetz *et al.* provides clear teaching for the use of fluorescent proteins in

exactly this context. With respect to newly added claims, specifically the embodiment that the "promoter is activated after differentiation of the stem cells", clearly the teaching for use of tissue specific promoters anticipates this limitation because ES cells are totipotent cells that do not normally express tissue specific genes until they are differentiated into that tissue.

With respect to the second point of analyzing the activity and using any tissue specific promoter in the context of evaluating development of the ES cell, again it is noted that Zernicka-Goetz *et al.* provides the specific motivation to use any tissue specific promoter, however does not provide any detailed guidance to the sequences or properties of specific tissue specific promoters. At the time of filing many tissue specific promoters were known, and specifically each of the Nkx-2.5, human alpha-actin or MLC-2V promoters were known and characterized as demonstrated by the cited references. Moreover, the pCX-GFP vector construct taught by Ikawa *et al.* containing the beta-actin and CD4 promoters were specifically used as a marker in transgenic studies. The indication in the e-mail from Dr. Ockabe (scientist in Dr. Ikawa's lab) that the construct may not work well in ES cells is noted, however the functionality of a tissue specific promoter would not be assessed in an ES cell, rather in a differentiated in which it is normally active as indicated in the e-mail. Moreover, it does not indicate that it does not work, rather that it may not work well. Further, the potential problem of using wild type GFP as disclosed by Ikawa *et al.* is specifically discussed and remedied/bettered by the teaching Zernicka-Goetz *et al.* (page 1146, second column). Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). In this case, tissue specific promoters were known and characterized in the art prior to the instant

application. Moreover, to practice the instantly claimed method as claimed requires the teaching of the art to obtain any of these specific promoters encompassed by the claims. Given the motivation of Zernicka-Goetz *et al.* to use tissue specific promoters, the use of characterized tissue specific promoters known in the art at the time of filing to map the fate of cell differentiation would be obvious with a high expectation of success. There is nothing in the art of record that indicates that a tissue specific promoter behaves differently dependent on the cell into which it is inserted, and it would be expected that if it represents a tissue specific promoter that it would be active primarily in a differentiated representative of the tissue which normally drives expression of the promoter.

For the reasons above and of record, the rejection is maintained.

Conclusion

No claim is allowed.

Claims 41 and 63 are free of the art of record because the art fails to teach the specific vector deposited as DSM11633.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

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